

10613482
10/9603

(12) UK Patent Application (19) GB (11) 2 185 255 (13) A

(43) Application published 15 Jul 1987

(21) Application No 8700662
(22) Date of filing 13 Jan 1987
(30) Priority data
(31) 8600752 (32) 14 Jan 1986 (33) GB

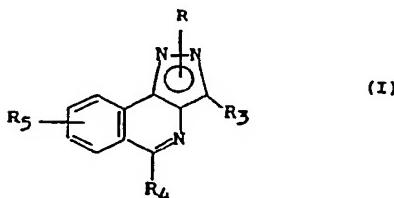
(51) INT CL⁴
C07D 471/04 A61K 31/47
(52) Domestic classification (Edition I):
C2C 213 214 220 226 22Y 246 247 250 252 25Y 305
30Y 313 31Y 339 339 776 77Y ZF
U1S 2416 C2C

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(56) Documents cited
None
(58) Field of search
C2C

(54) Pyrazolo-isoquinoline compounds

(57) Compounds of the formula I



[wherein

R represents a hydrogen atom, a C₁₋₈alkyl group or a C₂₋₈ alkenyl group (either of these groups being optionally substituted by a C₆₋₁₀ monocyclic or bicyclic aryl group, or represents a C₃₋₆ cycloalkyl group or a C₁₋₈ haloalkyl group;

R₃ represents a hydrogen atom, a C₁₋₈ alkyl group or a C₆₋₁₀ monocyclic or bicyclic aryl group;

R₄ represents a C₁₋₈ alkyl group or a C₂₋₈ alkenyl group (either of these groups being optionally substituted by a C₆₋₁₀ monocyclic or bicyclic aryl group, or represents a C₃₋₆ cycloalkyl group or a C₆₋₁₀ monocyclic or bicyclic aryl group (optionally substituted by a C₁₋₆ alkyl group or by a halogen atom); and

R₅ represents a hydrogen or halogen atom, a C₁₋₈ alkyl group, a C₁₋₈ alkoxy group or a nitro group] and acid addition salts thereof exhibit anti-inflammatory activity.

GB 2 185 255 A

SPECIFICATION

Chemical compounds

5 The present invention relates to pyrazolo[4,3-c]isoquinolines, to processes for their preparation, to their use as medicaments and to pharmaceutical compositions containing them.

According one feature of the invention there are provided compounds of formula I



[wherein

20 R represents a hydrogen atom, an alkyl group containing 1 to 8 carbon atoms or an alkenyl group containing 2 to 8 carbon atoms (either of these groups being optionally substituted by a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms), or represents a cycloalkyl group containing 3 to 6 carbon atoms or a straight-chained or branched haloalkyl group containing 1 to 8 carbon atoms;

25 R₃ represents a hydrogen atom, an alkyl group containing 1 to 8 carbon atoms or a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms; R₄ represents an alkyl group containing 1 to 8 carbon atoms or an alkenyl group containing 2 to 8 carbon atoms (either of these groups being optionally substituted by a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms), or represents a cycloalkyl group containing 3 to 6 carbon atoms or a

30 monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms (optionally substituted by an alkyl group containing 1 to 6 carbon atoms or by a halogen atom); and

35 R₅ represents a hydrogen or halogen atom, an alkyl group containing 1 to 8 carbon atoms, an alkoxy group containing 1 to 8 carbon atoms or a nitro group] and acid addition salts thereof.

The substituent R in formula I may be present in either the 1-position of the 2-position of the pyrazole ring. Thus, formula encompasses compounds of formula I'



45 and compounds of formula I"



55 (wherein

R₁ and R₂ each represents a hydrogen atom, an alkyl group containing 1 to 8 carbon atoms or an alkenyl group containing 2 to 8 carbon atoms (either of these groups being optionally substituted by a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms), or represents a cycloalkyl group containing 3 to 6 carbon atoms or a straight-chained or branched

60 haloalkyl group containing 1 to 8 carbon atoms).

The term "an alkyl group containing 1 to 8 carbon atoms" as used herein includes, for example, a methyl or ethyl group, or a straight-chained or branched propyl, butyl, hexyl or octyl group.

The term "an alkenyl group containing 2 to 8 carbon atoms" as used herein includes, for example, a vinyl, allyl, propen-2-yl, buten-2-yl, buten-3-yl, penten-3-yl, penten-4-yl, octen-2-yl,

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octen-3-yl, octen-4-yl or octen-5-yl group.

The term "a cycloalkyl group containing 3 to 6 carbon atoms" as used herein refers to a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

The term "a straight-chained or branched haloalkyl group containing 1 to 8 carbon atoms" as used herein includes, for example, a chloromethyl, chloroethyl, bromomethyl or bromoethyl group, or a straight-chained or branched chloropropyl, chlorobutyl, chloropentyl, chlorooctyl, bromopropyl, bromobutyl, bromopentyl or bromooctyl group.

The term "a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms (optionally substituted by an alkyl group containing 1 to 6 carbon atoms)" as used herein includes, for example, a phenyl, naphthyl, indenyl, 4-methylphenyl, 4-ethylphenyl, 4-propylphenyl, 2-methylnaphthyl, 2-ethylnaphthyl, 2-propylnaphthyl, 2-methylindenyl or 2-ethylindenyl group.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be the physiologically acceptable acid addition salts, but other salts may find use, for example in the preparation of compounds of formula I and the physiologically acceptable acid addition salts thereof. The expression "acid addition salts" as used herein includes salts formed with inorganic or organic acids. Suitable acids include, for example, hydrochloric, hydrobromic, hydriodic, nitric, sulphuric, phosphoric, propionic, acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkanesulphonic (e.g. methanesulphonic) or arylsulphonic (e.g. benzene-sulphonic) acids.

20 The compounds according to the invention possess interesting pharmacological properties and exhibit, in particular, anti-inflammatory activity.

Preferred compounds according to the invention include those compounds of formula I wherein R represents a hydrogen atom or a methyl group;

R₃ represents a methyl or phenyl group; and

25 R₄ represents a methyl group, or a phenyl group (optionally substituted by a methyl group or by a halogen atom), and acid addition salts thereof.

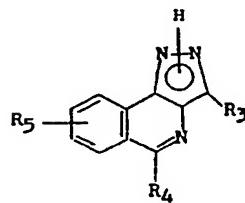
Particularly preferred compounds according to the invention include:

3-methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline;

30 1,3-dimethyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline; and
2-ethyl-3-methyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline,
and acid addition salts thereof.

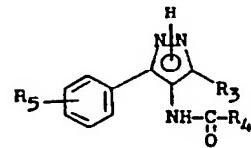
The compounds according to the invention may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

35 A. For the preparation of a compound of formula I wherein R represents a hydrogen atom (i.e. for the preparation of a compound of formula IA



wherein R₃, R₄ and R₅ are as hereinbefore defined):

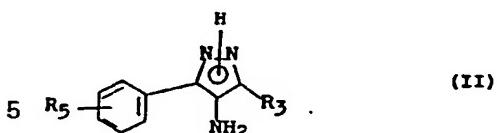
Cyclisation of a compound of formula IV



(wherein R₃, R₄ and R₅ are as hereinbefore defined) by heating in the presence of polyphosphoric acid.

The cyclisation is preferably effected at a temperature of from 200 to 300°C.

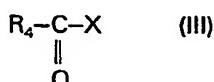
60 The compound of formula IV may conveniently be prepared by reacting a compound of formula II



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(wherein R_3 and R_5 are as hereinbefore defined) with a compound of formula III

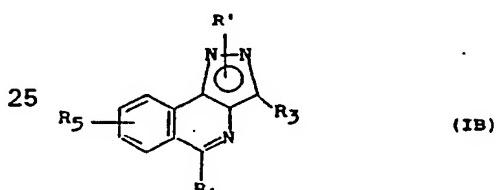
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15 (wherein R₄ is as hereinbefore defined; and X represents a halogen atom, preferably a chlorine atom).

The reaction is preferably effected in the presence of a halogenated organic solvent such as, for example, chloroform.

B. For the preparation of a compound of formula I wherein R does not represent a hydrogen atom (i.e. for the preparation of a compound of formula IB)

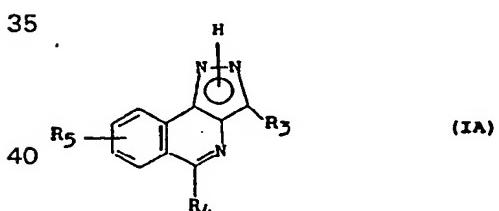


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30 wherein R' is as hereinbefore defined for R with the exception of a hydrogen atom; and R₃, R₄ and R₅ are as hereinbefore defined);

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Reaction of a compound of formula IA



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(wherein R₁, R₄ and R₅ are as hereinbefore defined) with a compound of formula V

45



(wherein R' is as hereinbefore defined; and Hal represents a halogen atom, preferably an iodine atom)

50 The reaction is preferably effected in the presence of an alkali metal hydride, e.g. sodium hydride, and is also conveniently carried out in the presence of an organic solvent, preferably dimethylformamide. 50

The compounds of formula I obtained from the processes according to the invention are basic in character and may subsequently, if desired, be converted into the acid addition salts thereof, particularly the physiologically acceptable acid addition salts thereof with inorganic or organic acids, for example by conventional methods such as by reacting the compounds as bases with a solution of a stoichiometric amount of the corresponding acid in a suitable solvent. Such salts may be prepared *in situ* in the reaction mixture without the necessity for intermediate isolation of the free bases themselves. Conversely the acid addition salts of the compounds of formula I

obtained may, if desired, subsequently be converted into compounds of formula I or into acid addition salts thereof.

The compounds of formula II, used as starting materials in the above process, may be synthesised by the method described in *Ann. Chim. (Rome)*, 1959, 49, 720.

inflammatory activity. In view of their pharmacological effects, the compounds according to the invention are suitable for use as medicaments. The present invention therefore provides compounds of formula I and physiologically acceptable acid addition salts thereof for use in the treatment of inflammatory states.

- 5 According to a still further feature of the present invention there are provided pharmaceutical compositions containing, as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically acceptable acid addition salt thereof in association with one or more inert pharmaceutical carriers and/or excipients.

For pharmaceutical administration the compounds of formula I and their physiologically acceptable acid addition salts may be incorporated into compositions currently used in human medicine for oral, rectal, parenteral or topical administration, optionally in combination with other active ingredients. The pharmaceutical compositions may be in either solid or liquid form, using carriers and excipients conventionally employed in the pharmaceutical art. Preferred forms include, for example, plain tablets, coated tablets, capsules, granules, ampoules, suppositories, syrups, creams, ointments and solutions, e.g. for injection, prepared in traditional manner.

The active ingredient(s) may be used in conjunction with excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, animal or vegetable fats, paraffin derivatives, various wetting, dispersing or emulsifying agents and/or preservatives.

- 20 Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units contain from 20 to 300 mg, preferably from 20 to 50 mg, of active ingredient. The total daily dosage will vary depending on the compound used but will generally be within the range of from 20 to 50 mg of active ingredient for oral administration to adult humans. This dosage may, however, also be varied

- 25 according to the subject treated, the route of administration and the complaint concerned.

According to a yet further feature of the present invention there is provided a method for the treatment of a patient suffering from, or susceptible to, inflammatory states which comprises administering to the said patient an effective amount of a compound of formula I as hereinbefore defined or a physiologically acceptable acid addition salt thereof.

- 30 The following non-limiting Examples serve to illustrate the present invention more fully.

Example 1: 3-Methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline

Method A

Step A:

- 35 To a stirred solution of 3-methyl-5-phenyl-4-pyrazolamine (10 g) in chloroform (100 ml) was added benzoyl chloride (10 g), and the resulting mixture was stirred at room temperature for half an hour. The solid material was filtered off, washed with chloroform and stirred for 1 hour in aqueous sodium bicarbonate (10%, 100 ml). The resulting solid product was filtered off, washed with water and dried to give *N*-(3-methyl-5-phenyl-4-pyrazolyl)benzamide (12 g), m.p. 240–3°C,

40 ν_{max} 3390 and 1655 cm^{-1} .

Step B:

- A mixture of N-(3-methyl-5-phenyl-4-pyrazolyl)benzamide (9 g) and polyphosphoric acid (90 g) was heated at 200–300°C for 15–30 min, cooled to 100°C and poured into water. The solution 45 was treated with charcoal, filtered through Celite and neutralised with concentrated aqueous ammonia. The precipitated solid was filtered, washed and dried, and the product was recrystallised from ethanol to give 3-methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline (7 g), m.p. 278–80°C, listed as Example 1 in Table 1.

By using the appropriate 4-pyrazolamines and acid chlorides the compounds of Examples 4, 5, 50 6, 7 and 10 were also prepared.

Example 4: 3,5-Dimethyl-1H-pyrazolo[4,3-c]isoquinoline

Example 5: 3-Methyl-5-(4-methylphenyl)-1H-pyrazolo[4,3-c]isoquinoline

Example 6: 5-Methyl-3-phenyl-1H-pyrazolo[4,3-c]isoquinoline

- 55 *Example 7: 5-(4-Chlorophenyl)-3-methyl-1H-pyrazolo[4,3-c]isoquinoline*

Example 10: 5-Ethyl-3-methyl-1H-pyrazolo[4,3-c]isoquinoline

Examples 8 and 9: 1,3-Dimethyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline and 2,3-dimethyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline

Method B

- 60 A suspension of 3-methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline (5 g) and sodium hydride (80%, 0.5 g) in dimethylformamide (50 ml) was stirred at room temperature until a clear solution was obtained. Iodomethane (2 ml) was added and 20 minutes later the solution was diluted with water to crystallise a colourless solid which was filtered off, washed and dried (5 g). The solid was subjected to HPLC on silica, eluting with ethyl acetate-hexane (15:85), to give firstly 1,3-

65 *dimethyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline* (2.4 g) (Example 8), m.p. 171–3°C, and sec-

65

only 2,3-dimethyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline (2.2 g) (Example 9), m.p. 188-90°C.

The structural assignments were based on an observed Nuclear Overhauser Effect between the 1-methyl group and the 9-hydrogen atom in the compound of Example 8.

By using the appropriate alkyl iodide or bromide the compounds of Examples 2, 3 and 11
5 were also prepared.

5

Example 2: 1-(3-Chloropropyl)-3-methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline

Example 3: 2-(3-Chloropropyl)-3-methyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline

Example 11: 2-Ethyl-3-methyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline

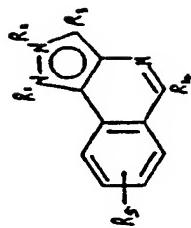


TABLE I

Ex	R_1	R_2	R_3	R_4	R_5	IR (KBr) cm^{-1} ν ₁₀₋₁₄	mp (°C)	Formula	Calc./Found (%)			
									H-NH	C	N	X
1	-	-	cH ₃	◎	-	A 83 1438	1620, 1500, 1480 1460	C ₁₇ H ₁₅ N ₃	259.3	78.74 78.6	5.05 5.1	16.20 16.4
2	c1(cH ₂) ₃	-	cH ₃	◎	-	B 20 1460, 1440	1618, 1500, 1473 1462, 1440	C ₂₀ H ₁₈ CN ₃	235.4	71.53 71.1	5.40 5.4	12.51 12.4
3	-	c1(cH ₂) ₃	cH ₃	◎	-	B 24 1460, 1440	1620, 1545, 1500 1462, 1440	C ₂₀ H ₁₈ CN ₃	235.4	71.53 71.5	5.40 5.3	12.51 12.4
4	-	-	cH ₃	cH ₃	-	A 57 1427	1627, 1500, 1483 1439	C ₁₂ H ₁₅ N ₃	197.2	73.08 73.41	5.63 5.87	21.30 21.56
5	-	-	cH ₃	cH ₃	-	A 63 1439, 1420, 1400	1638, 1492, 1480 1439, 1420, 1400	C ₁₈ H ₁₅ N ₃	273.3	79.10 79.10	5.94 5.94	15.36 15.36
6	-	-	cH ₃	◎	-	A 86 1462	1603, 1495, 1467 1500, 1460, 1437	C ₁₇ H ₁₅ N ₃	259.3	70.74 70.74	5.05 5.05	16.20 16.20
7	-	-	cH ₃	◎	-	A 58 1420	1629, 1592, 1559 1500, 1460, 1437	C ₁₇ H ₁₂ CN ₃	293.7	69.46 69.17	4.09 4.28	14.30 14.14
8	cH ₃	-	cH ₃	◎	-	B 46 1460, 1440, 1420	1615, 1498, 1477 1473, 1439	C ₁₆ H ₁₅ N ₃	273.3	79.10 79.0	5.53 5.6	15.37 15.3
9	-	cH ₃	cH ₃	◎	-	B 42 1473, 1439	1612, 1532, 1490 1473, 1439	C ₁₆ H ₁₅ N ₃	273.3	79.10 79.05	5.93 5.6	15.37 15.2
10	-	-	cH ₃	cH ₃	-	A 24 1441, 1420, 1410	1661, 1629, 1592 1520, 1500, 1459 1440	C ₁₃ H ₁₅ N ₃	211.3	73.09 73.49	6.21 6.02	19.88 14.56
11	-	c ₂ H ₅	cH ₃	◎	-	B 23 1531, 1495, 1475	1610, 1585, 1567 1531, 1495, 1475	C ₁₉ H ₁₆ N ₃	267.4	79.40 79.39	6.33 6.02	14.61 14.56

Example 12: Tablets were prepared according to the formulation:

—compound of Example 1 : 50 mg
 —excipient q.s. for one tablet up to : 300 mg
 (details of excipient: lactose, starch, talc, magnesium stearate). 5

Example 13:

Tablets were prepared according to the formulation:

10 —compound of Example 8 : 50 mg
 —excipient q.s. for one tablet up to : 300 mg
 (details of excipient: lactose, starch, talc, magnesium stearate). 10

Example 14:

A dosed aerosol was prepared delivering per dose:

20 —product of Example 1 : 10 mg
 —emulsifier : 0.15 mg
 —propellant : 50 mg 20

Example 15:

A syrup was prepared according to the formulation:

25 —product of Example 11 : 50 mg
 —flavouring and sweetening
 —excipient q.s.p. : 100 ml 25

30 BIOLOGICAL ACTIVITY

Inhibition of the synthesis of 5-lipoxygenase and cyclooxygenase products by guinea-pig peritoneal neutrophils was studied using minor modifications of the method of Harvey and Osborne (*J. Pharmacol. Meth.*, 1983, 9, 147). The results displayed in Table 2 demonstrate the micromolar concentrations of test compounds which are required to inhibit the synthesis of 5-HETE and 35 thromboxane B₂ by 50% compared to control (IC₅₀ μM).

The anti-oedematous properties of the compounds were preliminarily assessed by modification of the carrageenin-induced oedema procedure (*Proc. Soc. Exp. Biol. Med.*, 1962, 11, 544) following oral administration to male Wistar rats. The results displayed in Table 2 demonstrate the percentage inhibitions by weight compared to control after a dose of 20 and 100 mg/kg 40 p.o. 40

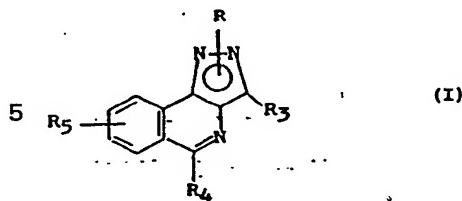
TABLE 2

Example	Inhibition of 5-HETE (IC ₅₀ μM)	Inhibition of Thromboxane B ₂ (IC ₅₀ μM)	% Inhibition of Rat Paw Oedema at 20 mg/kg and 100 mg/kg	
45				
1	3.1	3.6	48	31
2			24	
50				
4	>10	>10	6	49
5	>10	4.2	1	20
6	>10	>10	6	16
7	>10	>10	12	25
8	7.6	0.22	15	43
55				
9	>10	>10	18	38
10	>10	>10	14	35
11	10	0.15	34	44

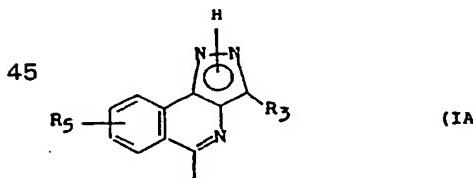
CLAIMS

60 1. Compounds of formula I

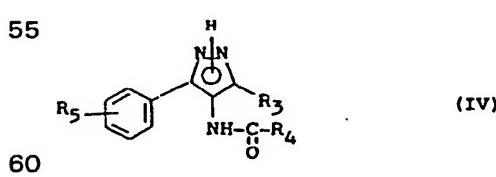
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- 10 [wherein
R represents a hydrogen atom, an alkyl group containing 1 to 8 carbon atoms or an alkenyl group containing 2 to 8 carbon atoms (either of these groups being optionally substituted by a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms), or represents a cycloalkyl group containing 3 to 6 carbon atoms or a straight-chained or branched haloalkyl group containing 1 to 8 carbon atoms;
- 15 R₃ represents a hydrogen atom, an alkyl group containing 1 to 8 carbon atoms or a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms;
- 20 R₄ represents an alkyl group containing 1 to 8 carbon atoms or an alkenyl group containing 2 to 8 carbon atoms (either of these groups being optionally substituted by a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms), or represents a cycloalkyl group containing 3 to 6 carbon atoms or a monocyclic or bicyclic aryl group containing 6 to 10 carbon atoms (optionally substituted by an alkyl group containing 1 to 6 carbon atoms or by a halogen atom); and
- 25 R₅ represents a hydrogen or halogen atom, an alkyl group containing 1 to 8 carbon atoms, an alkoxy group containing 1 to 8 carbon atoms or a nitro group] and acid addition salts thereof.
2. Compounds of formula I as claimed in claim 1 wherein
R represents a hydrogen atom or a methyl group;
R₃ represents a methyl or phenyl group; and
- 30 R₄ represents a methyl group or a phenyl group optionally substituted by a methyl group or by a halogen atom;
and acid addition salts thereof.
3. 3-Methyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline;
1,3-dimethyl-5-phenyl-1H-pyrazolo[4,3-c]isoquinoline; and
- 35 2-ethyl-3-methyl-5-phenyl-2H-pyrazolo[4,3-c]isoquinoline;
and acid addition salts thereof.
4. Physiologically acceptable acid addition salts of compounds of formula I as defined in claim 1.
5. Compounds as claimed in claim 1 as herein specifically disclosed in any one of Examples 1 to 11.
- 40 6. A process for the preparation of a compound of formula 1A



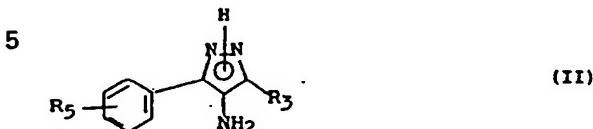
45 (wherein R₃, R₄ and R₅ are as defined in claim 1) which comprises the cyclisation of a compound of formula IV



50 (wherein R₃, R₄ and R₅ are as defined in claim 1) by heating in the presence of polyphosphoric acid.

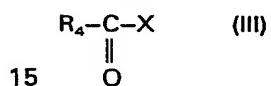
55 7. A process as claimed in claim 6 wherein the cyclisation is effected at a temp rature of 0 to 300°C.

8. A process as claimed in claim 6 or claim 7 wherein the compound of formula IV is prepared by reacting a compound of formula II



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10 (wherein R₃ and R₅ are as defined in claim 1) with a compound of formula III



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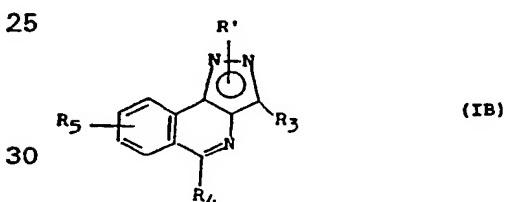
(wherein R₄ is as defined in claim 1; and X represents a halogen atom).

9. A process as claimed in claim 8 wherein in the compound of formula III X represents a chlorine atom.

20 10. A process as claimed in claim 8 or claim 9 wherein the reaction between the compound of formula II and the compound of formula III is effected in the presence of a halogenated organic solvent.

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11. A process for the preparation of a compound of formula 1B

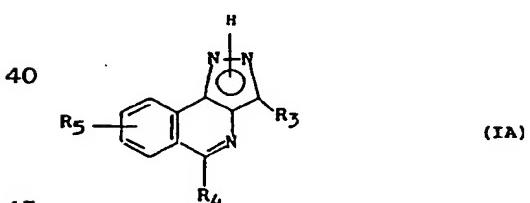


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30 wherein R' is as defined for R in claim 1 with the exception of a hydrogen atom; and R₃, R₄ and R₅ are as defined in claim 1)

35 which comprises reaction of a compound of formula IA

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45 (wherein R₃, R₄ and R₅ are as defined in claim 1) with a compound of formula V



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(wherein R' is as defined above; and Hal represents a halogen atom).

12. A process as claimed in claim 11 wherein in the compound of formula V Hal represents an iodine atom.

55 13. A process as claimed in claim 11 or claim 12 wherein the reaction of the compound of formula 1A with the compound of formula V is effected in the presence of an alkali metal hydride.

55

14. A process as claimed in anyone of claims 11 to 13 wherein the reaction of the compound of formula 1A with the compound of formula V is carried out in the presence of an organic solvent.

60 15. A process as claimed in claim 14 wherein the reaction of the compound of formula 1A with the compound of formula V is carried out in the presence of dimethylformamide.

60

16. A process as claimed in any one of claims 6 to 15 wherein a compound of formula I initially obtained is subsequently converted into an acid addition salt thereof and/or an acid addition salt of a compound of formula I is subsequently converted into a compound of formula

65 I.

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17. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.
18. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 11.
- 5 19. Compounds of formula I as defined in claim 1 and acid addition salts thereof whenever prepared by a process as defined in any one of claims 6 to 18. 5
20. Compounds as claimed in any of claims 1 to 5 for use in therapy.
21. The use of a compound as claimed in any one of claims 1 to 5 for the manufacture of an anti-inflammatory medicament.
- 10 22. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier and/or excipient. 10
23. Compositions as claimed in claim 22 wherein the active ingredient comprises a compound as defined in any one of claims 2 to 5.
- 15 24. Compositions as claimed in claim 22 or claim 23 in the form of dosage units. 15
25. Compositions as claimed in claim 24 wherein each dosage unit contains from 20 to 300 mg of active ingredient.
26. Compositions as claimed in claim 25 wherein each dosage unit contains from 20 to 50 mg of active ingredient.
- 20 27. Pharmaceutical compositions as claimed in claim 22 substantially as herein described. 20
28. Pharmaceutical compositions substantially as herein described in any one of Examples 12 to 15.
29. Each and every novel method, process, compound and composition herein disclosed.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon) Ltd, Dd 8991685, 1987.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

Serial No., 10/613,482
Filing Date: 07/03/2003
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DEAV2002/0045 US NP